REMARKS

Claims 1-39 are pending. Claims 2-39 are withdrawn. Claim 1 stands rejected.

The Amendments to the Specification correct typographical and grammatical errors.

By this Amendment, claims 1-12, 14-23, and 31-39 are canceled without prejudice. New claims 40 and 41 are added. Claim 40 replaces claim 1, reciting limitations discussed during the interview described below and deleting reference to non-elected embodiments. New claim 41 replaces non-elected claim 12, deleting reference to non-elected embodiments; for the reasons to be advanced, applicants respectfully request that the Examiner consider new claim 41 and dependent claims 13 and 24-30. The claims added and amended are fully supported in the application as filed; no new matter has been added.

Applicants confirm the election of Group I where the dye is a cyanine and E is hydrogen.

Applicants thank the Examiner for the courtesy of a telephone interview with applicants' undersigned representative on December 6, 2002. During the interview, applicants proposed amending claim 1 to recite an *in vivo* administrable form of the composition. Applicants have done this in new claim 40, and have also deleted reference to non-elected embodiments. Applicants believe this amendment overcomes the art rejections, as analyzed below. Applicants also respectfully request rejoinder of method claims directed to the elected embodiment (new claim 41 and

dependent claims 13 and 24-30). These claims recite performing a phototherapeutic procedure during which the dye-azide is administered. Because the method is limited to administration of the specific dye-azide elected, applicants respectfully request that these claims also be examined.

Applicants respectfully request reconsideration of the outstanding rejections for the following reasons.

CLAIM REJECTIONS UNDER 35 U.S.C. § 102

Claim 1 is rejected under 35 U.S.C. § 102(b) as anticipated by each of Pochinok, Ol'shevskaya, Clecak, and Leung.

New claim 40 replaces claim 1 as previously described; applicants will refer to new claim 40 in responding to the rejections.

New claim 40 recites a dye-azide composition in a pharmaceutically acceptable formulation. Applicants further assert that one skilled in the art appreciates that a pharmaceutically acceptable formulation requires at least a physiological solvent that is compatible or rendered compatible with the body, for example, by adding one or more buffers, by having a sterile solution for an injectable, etc.

Pochinok discloses the visible spectra of cyanines I-IV. Ol'shevskaya discloses photodecomposiion of azide derivatives of cyanine dyes. Clecak discloses a photoresist composition used in photography. Leung discloses dyes used for histochemical staining, which is an *in vitro* use. None of these references disclose a composition of the recited organic azide in a pharmaceutically acceptable formulation.

Attached hereto is a marked-up version of the changes made to the claims by the current Amendment. The attached page is captioned "Version with Markings to Show Changes Made."

CONCLUSION

For the foregoing reasons, applicants submit that all claims are patentable and a Notice of Allowance is respectfully requested.

Applicants do not believe that any fees are due in connection with this Amendment. However, should any additional fees or surcharges be deemed necessary, the Examiner has authorization to charge fees or credit any overpayment to Deposit Account No. 23-3000.

The Examiner is invited to contact the undersigned attorney with any questions or remaining issues.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Please replace the paragraph beginning at page 2, line 1, with the following rewritten paragraph:

Phototherapy has been in existence for many centuries and has been used to treat various skin surface ailments. As early as 1400 B.C. in India, plant extracts (psoralens), in combination with sunlight, were used to treat vitiligo. In 1903, Von Tappeiner and Jesionek[,] used eosin as a photosensitizer for treating skin cancer, lupus of the skin, and condylomata of female genitalia. Over the years, the combination of psoralens and ultraviolet A (low-energy) radiation has been used to treat a wide variety of dermatological diseases and manifestations including psoriasis, parapsoriasis, cutaneous T-cell lymphoma, eczema, vitiligo, areata, and neonatal bilirubinemia. Although the potential of cancer phototherapy has been recognized since the early 1900's, systematic studies to demonstrate safety and efficacy began only in 1967 with the treatment of breast carcinoma. In 1975, Dougherty et al. conclusively established that long-term cure is possible with photodynamic therapy (PDT). Currently, phototherapeutic methods are also being investigated for the treatment of some cardiovascular disorders such as atherosclerosis and vascular restenosis, for the treatment of rheumatoid arthritis, and for the treatment of some inflammatory diseases such as Chron's disease.

Please replace the paragraph beginning at page 3, line 7, with the following rewritten paragraph:

Photosensitizers operate via two distinct mechanisms, termed Types 1 and 2. The type 1 mechanism is shown in the following scheme:

$$\text{SENSITIZER} \xrightarrow{[h\nu]\ \ \underline{h\nu}} (\text{SENSITIZER})^*$$

$$(\text{SENSITIZER})^* + \text{TISSUE} \rightarrow \text{TISSUE DAMAGE}$$

Type 1 mechanisms involve direct energy or electron transfer from the photosensitizer to the cellular components thereby causing cell death. Type 2 mechanisms involve two distinct steps, as shown in the following scheme:

$$\text{SENSITIZER} \xrightarrow{[h\nu]\ \ \underline{h\nu}} (\text{SENSITIZER})^*$$

$$(\text{SENSITIZER})^* + {}^3O_2\ (\text{Triplet Oxygen}) \rightarrow {}^1O_2\ (\text{Singlet Oxygen})$$

$${}^1O_2\ (\text{Singlet Oxygen}) + \text{TISSUE} \rightarrow \text{TISSUE DAMAGE}$$

In the first step, singlet oxygen is generated by energy transfer from the triplet excited state of the photosensitizer to the oxygen molecules surrounding the tissues. In the second step, collision of singlet oxygen with the tissues promotes tissue damage. In both Type 1 and Type 2 mechanisms, the photoreaction proceeds via the lowest triplet state of the sensitizer. Hence, a relatively long triplet lifetime is required for effective phototherapy. In contrast, a relatively short triplet lifetime is required to avoid photodamage to the tissue caused by photosensitizers.

Please replace the paragraph beginning at page 6, line 4, with the following rewritten paragraph:

The present invention discloses novel compounds including organic azides for phototherapy of tumors and other lesions. More specifically, the present invention discloses compounds having the formula

E----L----DYE----X-----N_3

wherein DYE is an aromatic or a heteroaromatic radical derived from the group consisting of cyanines, indocyanines, phthalocyanines, rhodamines, phenoxazines, phenothiazines, phenoselenazines, fluoresceins, porphyrins, benzoporphyrins, squaraines, corrins, croconiums, azo dyes, methine dyes, and indolenium dyes. E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholecystekinin receptor binding molecules, steroid receptor binding molecules, and carbohydrate receptor binding molecules. L is selected from the group consisting of $-(CH_2)_a-$, $-(CH_2)_bCONR^1-$, $-N(R^2)CO(CH_2)_c-$, $-OCO(CH_2)_d-$, $-(CH_2)_eCO_2-$, -OCONH-, $-OCO_2-$, -HNCONH-, -HNCSNH-, -HNNHCO-, $-OSO_2-$, $-NR^3(CH_2)_eCONR^4-$, $-CONR^5(CH_2)_fNR^6CO-$, and $-NR^7CO(CH_2)_gCONR^8-$. X is either a single bond or is selected from the group consisting of $-(CH_2)_h-$, -OCO-, -HNCO-, $-(CH_2)_iCO-$, and $-(CH_2)_jOCO-$. R^1 to R^8 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, -OH, C1-C10 polyhydroxyalkyl, C1-C10 alkoxyl, C1-C10 alkoxyalkyl, $-SO_3H$, $-(CH_2)_kCO_2H$, and $-(CH_2)_lNR^9R^{10}$. R^9 and R^{10} are independently selected from the group consisting of

hydrogen, C1-C10 alkyl, C5-C10 aryl, and C1-C10 polyhydroxyalkyl. [And a] A to l independently range from 0 to 10.

Please replace the paragraph beginning at page 7, line 3, with the following rewritten paragraph:

The present invention also discloses a method of performing a therapeutic procedure using the compounds of the present invention. An effective amount of organic azide photosensitizer having the formula

E----L----DYE----X-----N_3

is administered to a subject. In this formula, DYE is an aromatic or a heteroaromatic radical derived from the group consisting of cyanines, indocyanines, phthalocyanines, rhodamines, phenoxazines, phenothiazines, phenoselenazines, fluoresceins, porphyrins, benzoporphyrins, squaraines, corrins, croconiums, azo dyes, methine dyes, and indolenium dyes. E is a hydrogen atom or is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholecystekinin receptor binding molecules, steroid receptor binding molecules, and carbohydrate receptor binding molecules. L is selected from the group consisting of $-(CH_2)_a-$, $-(CH_2)_bCONR^1-$, $-N(R^2)CO(CH_2)_c-$, $-OCO(CH_2)_d-$, $-(CH_2)_eCO_2-$, -OCONH-, $-OCO_2-$, -HNCONH-, -HNCSNH-, -HNNHCO-, $-OSO_2-$, $-NR^3(CH_2)_eCONR^4-$, $-CONR^5(CH_2)_fNR^6CO-$, and $-NR^7CO(CH_2)_gCONR^8-$. X is either a single bond or is selected from the group consisting of $-(CH_2)_h-$, -OCO-, -HNCO-, $-(CH_2)_iCO-$, and

$-(CH_2)_jOCO-$. R^1 to R^8 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, -OH, C1-C10 polyhydroxyalkyl, C1-C10 alkoxyl, C1-C10 alkoxyalkyl, $-SO_3H$, $-(CH_2)_kCO_2H$, and $-(CH_2)_lNR^9R^{10}$. R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C5-C10 aryl, and C1-C10 polyhydroxyalkyl. [And a] A to l independently range from 0 to 10. Following administration, the photosensitizer is allowed to accumulate in target tissue which is exposed to a light of wavelength between 300 and 950 nm. This light has sufficient power and fluence rate to cause necrosis or apoptosis of the said target tissue.

Please replace the paragraph beginning at page 8, line 5, with the following rewritten paragraph:

In an alternative embodiment of the method [of the present invention], the compounds [of the present invention] may be used to perform a phototherapeutic procedure including the following steps. A homogeneous photosensitizing mixture consisting of two or more Type 1 agents is prepared. This photosensitizing mixture is allowed to accumulate in target tissue which is exposed to a light of wavelength between 300 and 950 nm with sufficient power and fluence rate to cause necrosis or apoptosis of the target tissue.

Please replace the paragraph beginning at page 8, line 12, with the following rewritten paragraph:

In another alternative embodiment of the method [of the present invention], the compounds [of the present invention] may be used to perform a

phototherapeutic procedure including the following steps. A homogeneous photosensitizing mixture consisting of two or more Type 2 (PDT) agents is prepared. This photosensitizing mixture is allowed to accumulate in target tissue which is exposed to light of wavelength between 300 and 950 nm with sufficient power and fluence rate to cause necrosis or apoptosis of the target tissue.

Please replace the paragraph beginning at page 8, line 19, with the following rewritten paragraph:

In a further alternative embodiment of the method [of the present invention], the compounds [of the present invention] may be used to perform a phototherapeutic procedure including the following steps. A heterogeneous photosensitizing mixture consisting of one or more Type 1 agents and one or more Type 2 agents is prepared. This photosensitizing mixture is allowed to accumulate in target tissue which is exposed to light of wavelength between 300 and 950 nm with sufficient power and fluence rate to cause necrosis or apoptosis of [said] the target tissue.

Please replace the paragraph beginning at page 11, line 1, with the following rewritten paragraph:

In an alternative embodiment, azides according to the present invention have the general formula 1 above wherein DYE is an aromatic or a heteroaromatic radical derived from the group consisting of cyanines, phthalocyanines, rhodamines, porphyrins, benzoporphyrins, and corrins; E is [a] selected from the group consisting of

octreotide and octreotate peptides, heat-sensitive bacterioendotoxin receptor binding peptides, carcinoembryonic antigen antibody (anti-CEA), bombesin receptor binding peptide, neurotensin receptor binding peptide, cholecystekinin receptor binding peptide, and estrogen steroids; L is selected from the group consisting of -HNCO-, -$CONR^1$-, -HNCSNH-, -HNNHCO-,-$(CH_2)_aCONR^1$-,-$CONR^1(CH_2)_aNR^2CO$-, and R^1 and R^2 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C1-C5 polyhydroxyalkyl; and a, b, and c independently range from 0 to 6.

Please replace the paragraph beginning at page 11, line 13, with the following rewritten paragraph:

These compounds operate by a dual mechanism as shown in Fig. 1. N_3 is the azide moiety that produces nitrene upon photoactivation and DYE is an aromatic chromophore that undergoes photosensitization and produces singlet oxygen for PDT. Aliphatic azido compounds can also be used for phototherapy, but may require high-energy light for activation unless the azide moiety is attached to a conjugated polyene system. L is a linker between the chromophore and the epitope. Epitope (E) is a particular region of the molecule that is recognized by, and binds to, the target site on the cell. An epitope is usually, but not always, associated with biomolecules, which includes hormones, amino acids, peptides, peptidomimetics, proteins, nucleosides, nucleotides, nucleic acids, enzymes, carbohydrates, glycomimetics, lipids, albumins, mono- and polyclonal antibodies, receptors, inclusion compounds such as cyclodextrins, and receptor binding molecules. Specific examples of biomolecules

include steroid hormones for the treatment of breast and prostate lesions, somatostatin, bombesin, and neurotensin receptor binding molecules for the treatment of neuroendocrine tumors, cholecystekinin (CCK) receptor binding molecules for the treatment of lung cancer, heat sensitive bacterioendotoxin (ST) receptor and carcinoembryonic antigen (CEA) binding molecules for the treatment of colorectal cancer, dihyroxyindolecarboxylic acid and other melanin producing biosynthetic intermediates for melanoma, integrin receptor and atheroscleratic plaque binding molecules for the treatment of vascular diseases, and amyloid plaque binding molecules for the treatment of brain lesions. Biomolecules for use in the present invention may also include synthetic polymers. Examples of synthetic polymers include polyaminoacids, polyols, polyamines, polyacids, oligonucleotides, aborols, dendrimers, and aptamers. Coupling of diagnostic and radiotherapeutic agents to biomolecules can be accomplished by methods well known in the art, as disclosed in Hnatowich et al., *Radioactive Labeling of Antibody: A simple and efficient method.* Science, 1983, 220, 613-615; A. Pelegrin et al., *Photoimmunodiagnosis with antibody-fluorescein conjugates: in vitro and in vivo preclinical studies.* Journal of Cellular Pharmacology, 1992, 3, 141-145; and U.S. Patent No. 5,714,342, each of which is expressly incorporated by reference herein in its entirety. Successful specific targeting of fluorescent dyes to tumors using antibodies and peptides for diagnostic imaging of tumors has been demonstrated by us and others, for example, in S.A. Achilefu et al., *Novel receptor-targeted fluorescent contrast agents for in vivo tumor imaging*, Investigative Radiology, 2000, 35(8), 479-485; B. Ballou et al., *Tumor labeling in vivo*

using cyanine-conjugated monoclonal antibodies. Cancer Immunology and Immunotherapy, 1995, 41, 257-263; and K. Licha et al., *New contrast agents for optical imaging: acid-cleavable conjugates of cyanine dyes with biomolecules.* In Biomedical Imaging: Reporters, Dyes, and Instrumentation, D.J. Bornhop, C. Contag, and E.M. Sevick-Muraca (Eds.), Proceedings of SPIE, 1999, 3600, 29-35, each of which is expressly incorporated by reference herein in its entirety. Therefore, the inventive receptor-targeted phototherapeutic agents are expected to be effective in the treatment of various lesions.

Please replace the paragraph beginning at page 13, line 7, with the following rewritten paragraph:

In the present invention, dual phototherapeutic effect involving both Type 1 and Type 2 mechanisms can be accomplished by incorporating the reactive intermediate precursors into a conventional PDT [dyes] dye and using a dual wavelength light source to effect the generation of reactive intermediates as well as the generation of singlet oxygen. In some cases it may be possible to activate both Type 1 and Type 2 mechanisms using same wavelength of light. Dyes containing azide group have been prepared previously, as in S. Sunthankar et al., *Reactive disperse dyes. 1. Reactivity involving nitrene intermediate from azido group.* Indian Journal of Chemistry, 1973, 11(5), 503-504, which is expressly incorporated by reference herein in its entirety.

Please replace the paragraph beginning at page 13, line 17, with the following rewritten paragraph:

In the process outlined in Fig. 1, the photoexcitation of the aromatic chromophore effects rapid intramolecular energy transfer to the azido group, resulting in bond rupture and production of nitrene and molecular nitrogen. The nitrogen that is released is in a vibrationally excited state, which may cause additional cellular injury.

IN THE CLAIMS:

Claims 1-12, 14-23, and 31-39 have been canceled without prejudice.

New claims 40 and 41 have been added.

The following claims have been amended:

13. (AMENDED) The method of claim [12] 41 further comprising the step of allowing said photosensitizer to accumulate in said target tissue.

24. (AMENDED) The method of claim [23] 41 wherein the effective amount of the organic azide photosensitizer administered to the target tissue is in a range of about 0.1 mg/kg body weight to about 500 mg/kg body weight.

26. (AMENDED) The method of claim [12] 41 wherein the organic azide photosensitizer is parenterally administered to the target tissue in a formulation including the organic azide photosensitizer and materials selected from the group

consisting of pharmaceutically acceptable buffers, emulsifiers, surfactants, and electrolytes.

28. (AMENDED) The method of claim [12] 41 wherein the organic azide photosensitizer is enterally administered to the target tissue in a formulation including the organic azide photosensitizer and materials selected from the group consisting of buffers, surfactants, emulsifiers, and thixotropic agents.

29. (AMENDED) The method of claim [12] 41 wherein the organic azide photosensitizer is topically administered to the target tissue in a formulation including the organic azide photosensitizer and materials selected from the group consisting of liquid excipients and semisolid excipients.

30. (AMENDED) The method of claim [12] 41 wherein the organic azide photosensitizer is administered in a form selected from the group consisting of an aerosol spray, a cream, a gel, and a solution.